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Protocol for the Examination of Specimens From Patients With Carcinoma of the Ampulla of Vater

Protocol applies to all intra-ampullary, peri-ampullary, and mixed intra- and peri-ampullary carcinomas. Well-differentiated neuroendocrine neoplasms (carcinoid tumors) are not included.

Based on AJCC/UICC TNM, 7th edition

Protocol web posting date: June 2012

Procedures

- Ampullectomy
- Pancreaticoduodenectomy (Whipple Resection)

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CAP Ampulla of Vater Protocol Revision History

Version Code

The definition of the version code can be found at www.cap.org/cancerprotocols.

Version: AmpullaVater 3.1.0.1

Summary of Changes

The following changes have been made since the February 2011 release.

Ampullectomy, Pancreaticoduodenectomy (Whipple Resection)

Histologic Type (select all that apply)

Adenocarcinoma subtypes and Small cell carcinoma were updated, as follows:

Histologic Type (select all that apply)

- Adenocarcinoma (not otherwise characterized, or select subtype below if applicable)
 - + Adenocarcinoma, pancreaticobiliary type
 - + Papillary adenocarcinoma
 - + Adenocarcinoma, intestinal type
- Mucinous adenocarcinoma
- Clear cell adenocarcinoma
- Signet-ring cell carcinoma
- Adenosquamous carcinoma
- Squamous cell carcinoma
- High-grade neuroendocrine carcinoma
 - Large cell neuroendocrine carcinoma
 - Small cell neuroendocrine carcinoma
- Other (specify): _____
- Carcinoma, not otherwise specified

Margins (select all that apply)

The following was added:

Other Margin(s) (required only if applicable)

Specify margin(s): _____

- Cannot be assessed
- Uninvolved by invasive carcinoma
- Involved by invasive carcinoma

Explanatory Notes

Histologic Type: Histologic types were updated, as detailed above.

References

Reference #6 was updated.

Surgical Pathology Cancer Case Summary

Protocol web posting date: June 2012

AMPULLA OF VATER: Ampullectomy, Pancreaticoduodenectomy (Whipple Resection)

Select a single response unless otherwise indicated.

Specimen (select all that apply)

Ampulla of Vater

Other organs received:

Stomach

Head of pancreas

Duodenum

Common bile duct

Gallbladder

Other (specify): _____

Not specified

Procedure

Ampullectomy

Pancreaticoduodenectomy (Whipple resection)

Other (specify): _____

Not specified

Tumor Site (Note A)

Intra-ampullary

Peri-ampullary

Papilla of Vater (junction of ampullary and duodenal mucosa)

Other (specify): _____

Cannot be determined

Not specified

Tumor Size (Note B)

Greatest dimension: ___ cm

+ Additional dimensions: ___ x ___ cm

Cannot be determined (see Comment)

Histologic Type (select all that apply) (Note C)

- ___ Adenocarcinoma (not otherwise characterized, or select subtype below if applicable)
- + ___ Adenocarcinoma, pancreaticobiliary type
 - + ___ Papillary adenocarcinoma
 - + ___ Adenocarcinoma, intestinal type
- ___ Mucinous adenocarcinoma
- ___ Clear cell adenocarcinoma
- ___ Signet-ring cell carcinoma
- ___ Adenosquamous carcinoma
- ___ Squamous cell carcinoma
- ___ High-grade neuroendocrine carcinoma
- ___ Large cell neuroendocrine carcinoma
 - ___ Small cell neuroendocrine carcinoma
- ___ Other (specify): _____
- ___ Carcinoma, not otherwise specified

Histologic Grade (Note D)

- ___ Not applicable (histologic type not usually graded)
- ___ GX: Cannot be assessed
- ___ G1: Well differentiated
- ___ G2: Moderately differentiated
- ___ G3: Poorly differentiated
- ___ G4: Undifferentiated
- ___ Other (specify): _____

Microscopic Tumor Extension (select all that apply)

- ___ Cannot be assessed
- ___ No evidence of primary tumor
- ___ Carcinoma in situ
- ___ Tumor limited to ampulla of Vater or sphincter of Oddi
- ___ Tumor invades duodenal wall
- ___ Tumor invades pancreas
- ___ Tumor invades peripancreatic soft tissues
- ___ Tumor invades extrapancreatic common bile duct
- ___ Tumor invades other adjacent organs or structures other than pancreas
(specify): _____

Margins (select all that apply) (Note E)Ampullectomy Specimen

- ___ Cannot be assessed
- ___ Margins uninvolved by invasive carcinoma
Distance of invasive carcinoma from closest margin: ___ mm
Specify margin (if possible): _____
- ___ Margins involved by invasive carcinoma
Specify margin(s) (if possible): _____
- ___ Not applicable

Pancreaticoduodenal Resection Specimen

If all margins uninvolved by invasive carcinoma:

Distance of invasive carcinoma from closest margin: ___ mm or ___ cm

Specify margin: _____

Proximal Mucosal Margin (Gastric or Duodenal)

- Cannot be assessed
- Uninvolved by invasive carcinoma
- Involved by invasive carcinoma
- Intramucosal carcinoma /adenoma not identified at proximal margin
- Intramucosal carcinoma/adenoma present at proximal margin

Distal Margin (Distal Duodenal or Jejunal)

- Cannot be assessed
- Uninvolved by invasive carcinoma
- Involved by invasive carcinoma
- Intramucosal carcinoma/adenoma not identified at distal margin
- Intramucosal carcinoma /adenoma present at distal margin

Pancreatic Retroperitoneal (Uncinate) Margin

- Not applicable
- Cannot be assessed
- Uninvolved by invasive carcinoma
- Involved by invasive carcinoma (tumor present 0-1 mm from margin)

Bile Duct Margin

- Not applicable
- Cannot be assessed
- Margin uninvolved by invasive carcinoma
- Margin involved by invasive carcinoma

Distal Pancreatic Resection Margin

- Not applicable
- Cannot be assessed
- Margin uninvolved by invasive carcinoma
- Margin involved by invasive carcinoma

Other Margin(s) (required only if applicable)

Specify margin(s): _____

- Cannot be assessed
- Uninvolved by invasive carcinoma
- Involved by invasive carcinoma

Lymph-Vascular Invasion (Note B)

- Not identified
- Present
- Indeterminate

+ Data elements preceded by this symbol are not required. However, these elements may be clinically important but are not yet validated or regularly used in patient management.

+ Perineural Invasion (Note B)

- + ___ Not identified
- + ___ Present
- + ___ Indeterminate

Pathologic Staging (pTNM) (Note F)

TNM Descriptors (required only if applicable) (select all that apply)

- ___ m (multiple primary tumors)
- ___ r (recurrent)
- ___ y (posttreatment)

Primary Tumor (pT)

- ___ pTX: Cannot be assessed
- ___ pT0: No evidence of primary tumor
- ___ pTis: Carcinoma in situ
- ___ pT1: Tumor limited to ampulla of Vater or sphincter of Oddi
- ___ pT2: Tumor invades duodenal wall
- ___ pT3: Tumor invades pancreas
- ___ pT4: Tumor invades peripancreatic soft tissues or other adjacent organs or structures

Regional Lymph Nodes (pN)

- ___ pNX: Cannot be assessed
- ___ pN0: No regional lymph node metastasis
- ___ pN1: Regional lymph node metastasis
- ___ No nodes submitted or found

Number of Lymph Nodes Examined

- Specify: ___
- ___ Number cannot be determined (explain): _____

Number of Lymph Nodes Involved

- Specify: ___
- ___ Number cannot be determined (explain): _____

Distant Metastasis (pM)

- ___ Not applicable
- ___ pM1: Distant metastasis
+ Specify site(s), if known: _____

+ Additional Pathologic Findings (select all that apply)

- + ___ None identified
- + ___ Dysplasia/adenoma
- + ___ Other (specify): _____

+ Ancillary Studies

- + Specify: _____
- + ___ Not performed

+ Clinical History (select all that apply) (Note G)

- + Familial adenomatous polyposis coli
- + Other (specify): _____
- + Not known

+ Comment(s)

Explanatory Notes

A. Anatomical Considerations

The ampulla of Vater is a complex structure that usually represents the confluence of the distal common bile duct and main pancreatic duct (Figure 1). In some individuals the ampulla includes only the distal common bile duct, with the pancreatic duct entering the duodenum elsewhere. The ampulla traverses the duodenal wall and opens into the duodenal lumen through a small mucosal elevation, the duodenal papilla (Figure 1). The ampulla is lined by pancreatico-biliary type ductal epithelium, whereas the duodenal papilla is covered by small intestinal epithelium. The sphincter of Oddi is part of the ampulla and consists of smooth muscle fibers that surround the distal end of the merged ducts.

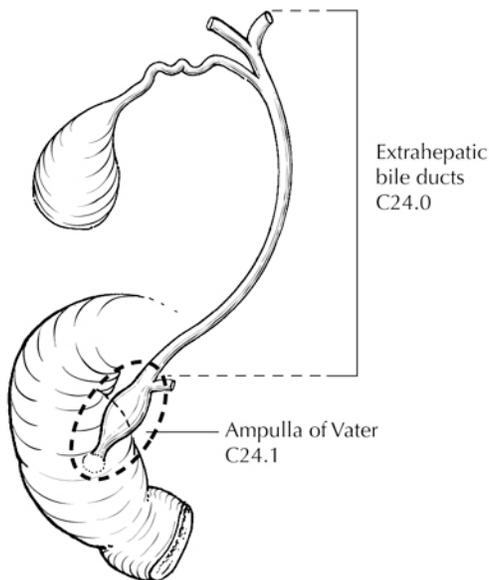


Figure 1. Anatomy of the ampulla of Vater. From Greene et al.¹³ Used with permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the *AJCC Cancer Staging Atlas* (2006) published by Springer Science and Business Media LLC, www.springerlink.com.

Tumors of the ampulla of Vater may arise in the ampulla (intra-ampullary type) or on the duodenal surface of the papilla (peri-ampullary type),¹ or may involve both the intra-ampullary and peri-ampullary regions (mixed type). Thus, ampullary tumors may show biliary and/or intestinal features. The origin of the tumor may be difficult, and occasionally impossible, to determine; the differential diagnosis includes carcinoma of the distal common bile duct, main pancreatic duct, and duodenum. Tumors may be exophytic or ulcerated.

B. Non-TNM Prognostic Factors

Although not included in the TNM staging system for tumors of the ampulla of Vater, tumor size has been shown to have independent prognostic significance for local recurrence.² In some series, pancreatic invasion, not tumor size, appears to be the more important prognostic factor.³

Lymph and small blood vessel invasion⁴ and perineural invasion⁵ have also been shown to be adverse prognostic factors.

C. Histologic Type

This protocol uses the following histologic classification but does not preclude the use of other histologic types or systems of classification. A modified classification of carcinomas of the gallbladder and

extrahepatic bile ducts published by the World Health Organization (WHO) that is applicable to the ampulla of Vater is as follows⁶:

WHO Classification of Ampullary Carcinoma

Adenocarcinoma
 Papillary adenocarcinoma#
 Adenocarcinoma, intestinal type
 Mucinous adenocarcinoma
 Clear cell adenocarcinoma
 Signet-ring cell carcinoma##
 Adenosquamous carcinoma
 Squamous cell carcinoma
 High-grade neuroendocrine carcinoma
 Large cell neuroendocrine carcinoma
 Small cell neuroendocrine carcinoma###
 Large cell neuroendocrine carcinoma
 Undifferentiated carcinoma###

The term "carcinoma, NOS (not otherwise specified)" is not part of the WHO classification.

Ampullary tumors of the papillary histologic type have been shown to have a favorable prognosis as compared with tumors of nonpapillary histologic types. Many of these tumors have a noninvasive exophytic growth pattern and hence a favorable prognosis. These tumors are more common in the gallbladder than in the ampullary region.¹

Signet-ring cell carcinomas are, by convention, classified as poorly differentiated (grade 3) adenocarcinomas.

Small cell carcinomas and undifferentiated (histologic type) carcinomas are assigned grade 4 (see below).

D. Histologic Grade

For nonpapillary adenocarcinomas, the following grading system is suggested:

GX	Grade cannot be assessed
G1	Well differentiated (greater than 95% of tumor composed of glands)
G2	Moderately differentiated (50% to 95% of tumor composed of glands)
G3	Poorly differentiated# (49% or less of tumor composed of glands)

Poor differentiation has been shown to be an adverse prognostic factor on univariate analysis in some, but not all, series.^{2,7}

Grade 4 carcinomas include both undifferentiated carcinomas (histologic type) and small cell carcinoma (high-grade neuroendocrine carcinomas) in the WHO classification (see above). Undifferentiated carcinomas should show less than 5% glandular structures.

E. Margins

Local recurrence from invasive carcinoma in the region of the pancreatic head, including ampullary cancers invading the pancreas, most often occurs at the uncinate margin of the pancreatic head (retroperitoneal margin). Because this is a critical margin, inking the retroperitoneal surface of the pancreas and submitting sections through the tumor at its closest approach to this margin is recommended. Complete en face sections through the distal pancreatic resection margin (representing the distal margin of the main pancreatic duct) and the resection margin of the common

bile duct should also be taken. Microscopically positive margins of resection (R1) have been shown to have an adverse impact on prognosis in ampullary carcinoma.⁸

F. TNM and Anatomic Stage/Prognostic Groupings

The TNM staging system for tumors of the ampulla of Vater of the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC) is recommended and shown below.⁹ The post-resection prognosis of a patient with ampullary carcinoma is primarily determined by the anatomic extent of disease as defined by the TNM classification and stage groupings.^{2,7,8}

By AJCC/UICC convention, the designation "T" refers to a primary tumor that has not been previously treated. The symbol "p" refers to the pathologic classification of the TNM, as opposed to the clinical classification, and is based on gross and microscopic examination. pT entails a resection of the primary tumor or biopsy adequate to evaluate the highest pT category, pN entails removal of nodes adequate to validate lymph node metastasis, and pM implies microscopic examination of distant lesions. Clinical classification (cTNM) is usually carried out by the referring physician before treatment during initial evaluation of the patient or when pathologic classification is not possible.

Pathologic staging is usually performed after surgical resection of the primary tumor. Pathologic staging depends on pathologic documentation of the anatomic extent of disease, whether or not the primary tumor has been completely removed. If a biopsied tumor is not resected for any reason (eg, when technically infeasible) and if the highest T and N categories or the M1 category of the tumor can be confirmed microscopically, the criteria for pathologic classification and staging have been satisfied without total removal of the primary cancer.

TNM Descriptors

For identification of special cases of TNM or pTNM classifications, the "m" suffix and "y" and "r" prefixes are used. Although they do not affect the stage grouping, they indicate cases needing separate analysis.

The "m" suffix indicates the presence of multiple primary tumors in a single site and is recorded in parentheses: pT(m)NM.

The "y" prefix indicates those cases in which classification is performed during or after initial multimodality therapy (ie, neoadjuvant chemotherapy, radiation therapy, or both chemotherapy and radiation therapy). The cTNM or pTNM category is identified by a "y" prefix. The ycTNM or ypTNM categorizes the extent of tumor actually present at the time of that examination. The "y" categorization is not an estimate of tumor before multimodality therapy (ie, before initiation of neoadjuvant therapy).

The "r" prefix indicates a recurrent tumor when staged after a documented disease-free interval and is identified by the "r" prefix: rTNM.

T Category Considerations

pTis. For ampullary carcinomas, "carcinoma in situ" (pTis) as a staging term includes cancer cells confined within the glandular basement membrane (high-grade dysplasia). The term "carcinoma in situ" is not widely applied to glandular neoplastic lesions in the gastrointestinal tract but is retained for tumor registry reporting purposes as specified by law in many states. Noninvasive ampullary carcinomas with a papillary growth pattern are classified as pTis.

N Category Considerations

Regional lymph node metastases have been shown to have independent significance as an adverse prognostic factor in multiple series.^{2,10,11} Although a minimum number of lymph nodes has not been determined for optimal staging, retrieval and examination of at least 10 lymph nodes is recommended for pancreaticoduodenectomy.

The regional nodes (Figure 2) may be subdivided as follows:

- Superior: Lymph nodes superior to head and body of pancreas
- Inferior: Lymph nodes inferior to head and body of pancreas
- Anterior: Anterior pancreaticoduodenal, pyloric, and proximal mesenteric lymph nodes
- Posterior: Posterior pancreaticoduodenal, common bile duct or pericholedochal, and proximal mesenteric nodes

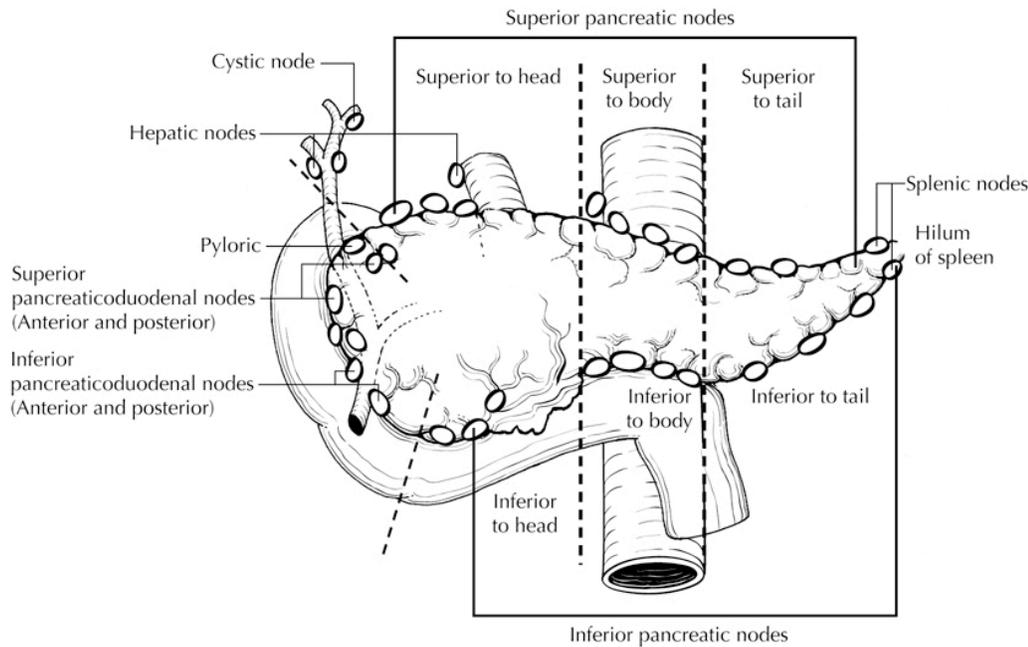


Figure 2. Regional lymph nodes of the ampulla of Vater. From Greene et al.¹³ Used with permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the *AJCC Cancer Staging Atlas* (2006) published by Springer Science and Business Media LLC, www.springerlink.com.

The following lymph nodes are also considered regional: hepatic artery nodes, infrapyloric nodes, subpyloric nodes, celiac nodes, superior mesenteric nodes, retroperitoneal nodes, and lateral aortic nodes. Tumor involvement of other nodal groups is considered distant metastasis. Anatomic division of regional lymph nodes is not necessary, but separately submitted lymph nodes should be reported as submitted.¹

Routine assessment of regional lymph nodes is limited to conventional pathologic techniques (gross assessment and histologic examination), and data are currently insufficient to recommend special measures to detect micrometastasis or isolated tumor cells. Thus, neither multiple levels of paraffin blocks nor the use of special/ancillary techniques such as immunohistochemistry are recommended for routine examination of regional lymph nodes.

Primary Tumor (T) (Figures 3-6)

- TX Cannot be assessed
- T0 No evidence of primary tumor
- Tis Carcinoma in situ
- T1 Tumor limited to ampulla of Vater or sphincter of Oddi
- T2 Tumor invades duodenal wall
- T3 Tumor invades pancreas

T4 Tumor invades peripancreatic soft tissues or other adjacent organs or structures other than pancreas

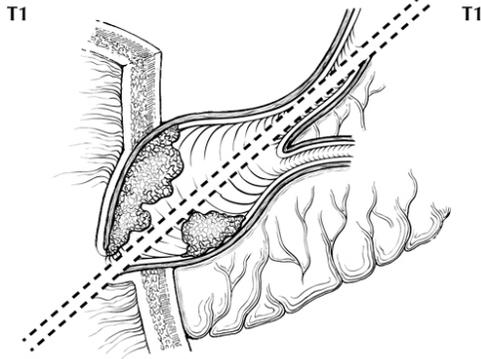


Figure 3. T1 tumors are limited to the ampulla of Vater (below the dotted line) or sphincter of Oddi (above the dotted line). From Greene et al.¹³ Used with permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the *AJCC Cancer Staging Atlas* (2006) published by Springer Science and Business Media LLC, www.springerlink.com.

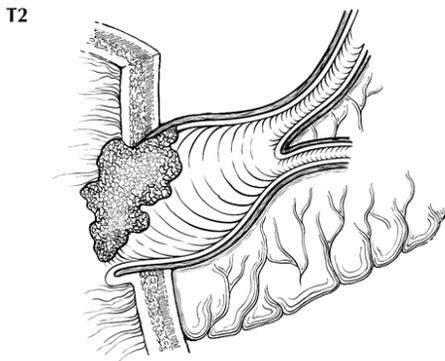


Figure 4. T2 tumors invade the duodenal wall. From Greene et al.¹³ Used with permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the *AJCC Cancer Staging Atlas* (2006) published by Springer Science and Business Media LLC, www.springerlink.com.

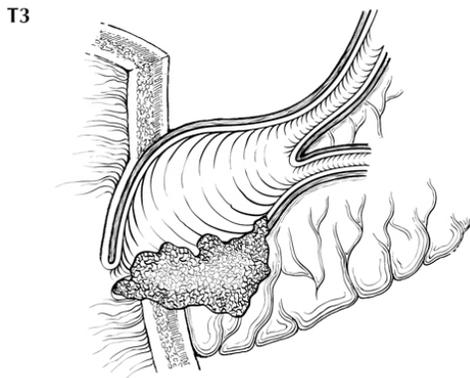


Figure 5. T3 tumors invade pancreas. From Greene et al.¹³ Used with permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the *AJCC Cancer Staging Atlas* (2006) published by Springer Science and Business Media LLC, www.springerlink.com.

T4

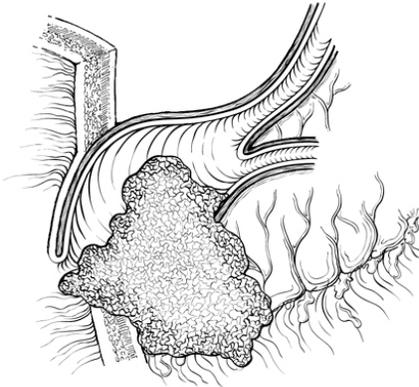


Figure 6. T4 tumors invade peripancreatic soft tissues or other adjacent organs or structures. From Greene et al.¹³ Used with permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the *AJCC Cancer Staging Atlas* (2006) published by Springer Science and Business Media LLC, www.springerlink.com.

Regional Lymph Nodes (N)

NX	Cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis

Distant Metastasis (M)

M0	No distant metastasis
M1	Distant metastasis

Stage Groupings

Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
Stage IIA	T3	N0	M0
Stage IIB	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
Stage III	T4	Any N	M0
Stage IV	Any T	Any N	M1

Vessel Invasion

By AJCC/UICC convention, vessel invasion (lymphatic or venous) does not affect the T category indicating local extent of tumor unless specifically included in the definition of a T category.

G. Relevant Clinical History

Ampullary adenomas are common in patients with familial adenomatous polyposis coli, and such patients are at increased risk for ampullary adenocarcinomas. Estimated lifetime incidence is roughly 12% for ampullary carcinoma in this population.¹²

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